# STANDARD OPERATING PROCEDURE 5 part 3
# Communication with Approval Bodies

| | | | |
|---|---|---|---|
| Version: | 3.0 | Effective Date: | 16 April 2024 |
| Issue Date: | 2 April 2024 | Review Date: | 16 April 2026 |
| Author: | Claire Daffern, Quality Assurance (QA) Manager, Warwick Clinical Trials Unit (WCTU) | | |
| WCTU Reviewers: | Bethany Foster, Clinical Trials Manager, WCTU | | |
| Sponsor Reviewers: | Mathew Gane, Research Governance & QA Manager, Research & Impact Services (R&IS) | | |
| WCTU approval: | Natalie Strickland, Head of Operations, WCTU | | |
| Sponsor approval: | Carole Harris, Deputy Director, (Head of Research Governance & Systems) (R&IS) | | |
| Review Lead: | WCTU QA Team | | |

Contents

| Revision Chronology: | Effective date: | Reason for change: |
|---|---|---|
| Version 3.0 | 16 April 2024 | Biennial review: Web links updated. Updates to information relating to CTIMPs which are approved via the Combined Review process. |
| Version 2.0 | 21 December 2021 | Update to section 4.3.7 on how to submit the study's final report to the HRA. Removal of references to CESP, addition of links to MHRA submission portal which is now in use. |
| Version 1.0 | 3 December 2020 | New SOP to detail requirements for maintaining contact with the bodies from whom initial study approvals were gained. This SOP has superseded previous versions of SOPs 5 and 6, which now detail initial applications and amendments to approved studies separately. |

# STANDARD OPERATING PROCEDURE 5 part 3
# Communication with Approval Bodies

## 1. Purpose and Scope

This Standard Operating Procedure (SOP) details the requirements for maintaining communications with the body/bodies which provided initial approval(s) for a research study.

Approvals will have been gained from an NHS Research Ethics Committee (REC) and the Health Research Authority (HRA) for all research studies conducted within the NHS, and from the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trials of Investigational Medicinal Products (CTIMPs).

For non-NHS research, research involving NHS staff as part of their role or for secondary use of anonymised patient data, approvals will have been obtained from the University's Biomedical and Scientific Research Ethics Committee (BSREC) and applicants should follow the process for submitting amendments as per their website.

This SOP is applicable to any researcher working on a University of Warwick sponsored research study or studies managed by WCTU sponsored by external organisations where use of Warwick SOPs has been agreed.

## 2. Definitions

| | |
|---|---|
| **Research Ethics Committee (REC)** | An independent body constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a study. They provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on the study protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the study participants. |
| **Regulatory Authorities** | Bodies having the power to regulate. In the ICH GCP guideline, the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities (CA) and in the UK, this is the MHRA. |
| **Medicines and Healthcare products Regulatory Agency (MHRA)** | The UK's regulator of medicines, medical devices and blood components for transfusion, responsible for ensuring their safety, quality and effectiveness. |
| **Development Safety Update Report (DSUR)** | A document which provides a comprehensive, annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation. |

## 3. Background

An NHS Research Ethics Committee (REC) has an important role to play throughout the lifetime of the study. It is required to give approval for the study to start (see SOP 5 part 1 'Gaining Initial Ethical Approval for Research Studies'), to receive annual progress reports, notification of amendments (see SOP 6 'Amendments to Approved Study Documents') and of serious adverse events (considered to be related to the study procedures and unexpected) and a declaration of the end of a study with a submission of the final report form.

The Health Research Authority (HRA) is responsible for NHS RECs and guidance for all these processes is available on their website.

It is a regulatory requirement for CTIMPs that the MHRA is also kept informed of the trials' progress throughout its lifetime. The MHRA requires that the Sponsor/Chief Investigator (CI) reports any SUSARs, submits annual progress reports for Type A trials or Development Safety Update Reports (DSUR) for Type B and C trials, informs them of the end of the trial and provides the final study report form.

For WCTU managed studies, these responsibilities are usually delegated to WCTU. If a study is managed by an external Clinical Trials Unit (CTU), this responsibility is likely to be delegated to the external CTU (and would be detailed in the contract/delegation of responsibilities document).

## 4. Procedure

### 4.1 Responsibilities

| | |
|---|---|
| **Chief Investigator (CI) (or delegate)** | • Submission of annual safety reports to the REC who provided the initial approval for the study<br>• Submission of annual progress report or DSUR to the MHRA (as applicable)<br>• Reporting safety issues where the SAE is deemed to be related to the intervention and is unexpected, within prescribed timelines<br>• Notification of any temporary suspension or early termination of a study<br>• Notification of the end of the study and submission of final study report form<br>• Posting study results on registry database |
| **Sponsor** | • Receipt of copies of annual safety reports, DSURs, expedited safety reports, notification of the end of the study and study results<br>• Oversight of the study |

### 4.2 When?

A progress report should be submitted to the NHS REC which provided the favourable opinion 12 months after the date on which the favourable opinion was given and annually thereafter until the end of the study. The first report should be submitted within 30 days of the first anniversary date on which the initial favourable opinion was given, and annually thereafter until the end of the study. (See section 4.3.1).

DSURs (Type B and C studies) or progress reports (Type A studies) are required to be submitted to the MHRA within 60 days of the anniversary of the first approval of a clinical trial application and a copy should also be sent to the relevant NHS REC for their information. (See section 4.3.2)

Expedited safety reports for Serious Adverse Events (SAEs) which are both related and unexpected must be submitted as soon as possible, but within a maximum of seven days in CTIMPs for SAEs which are fatal or life-threatening. SAEs which are categorised as one of the other 'serious' criteria must be submitted within 15 days (for CTIMPs and all other studies). (See section 4.3.3)

End of study notifications must be submitted within 90 days of the protocol stated end of study, or within 15 days if the study was temporarily suspended or terminated early. (See sections 4.3.4 – 4.3.6)

Study results must be sent to HRA (see section 4.3.7) and uploaded onto the relevant study registration website within twelve months of the notified end date of the study.

## 4.3 How?

### 4.3.1 Annual Progress Reports

Reports can be prepared by the CI or their delegate but must be signed by the CI. For University of Warwick sponsored studies, reports should also be submitted to the Sponsor's Office via sponsorship@warwick.ac.uk

There are separate forms for submitting progress reports, depending on the type of research:

- Annual progress report form for clinical trials of investigational medicinal products (CTIMPs)
- Annual progress report form for all other research
- Annual Report form for Research Databases
- Annual Report form for Research Tissue Banks

Forms should be completed in typescript and signed by the Chief Investigator.

An electronic copy should be emailed to the relevant REC.

Further details of how to submit annual reports can be found on the HRA website HRA guidance on submission of annual progress reports

For Warwick sponsored studies approved by BSREC, the R&IS governance team will send study leads a link to their Annual Progress Report (APR) form one month prior to the anniversary date of their approval and annually thereafter until the study team notify the sponsor's office that the project is complete.

### 4.3.2 Development Safety Update Report (DSUR)

In addition to the expedited reporting required for Suspected Unexpected Serious Adverse Reactions (SUSARs) as detailed in 4.3.3, for **Type B and C** CTIMPs a DSUR must be submitted once a year throughout the trial or on request. This report should take into account all data accrued and any new available safety information received during the reporting period. (See SOP 5 part 2 for more detail on trial categories).

Trials approved via the Combined Review process must submit their DSURs via the Integrated Research Application System (IRAS). A copy of the DSUR should also be sent to the relevant NHS REC and Sponsor's Office.

Trials approved outside of the Combined Review process must submit the DSUR via the MHRA Submissions portal. Select 'Development Safety Update Report' as the regulatory activity and 'original submission' from the regulatory sub activity drop down list. An acknowledgment of receipt of the report will be generated in the system and emailed to the person making the submission.

The data lock point for data to be included in the DSUR should be the anniversary date of the original MHRA approval. Data received in the year prior to this should be included. Full reconciliation of SAE data must be performed and documented in advance of DSUR line listing production.

Reports are due for submission within 60 calendar days of the anniversary of the initial trial approval. For clinical trials which have completed their intervention period (the participants are no longer receiving the trial IMP), and long-term follow-up is the only ongoing activity, completion of DSUR section 12.2 on long term follow-up may be the only section required.

MHRA fees include charges to annual safety reports - which are applicable to both Annual Progress Reports and DSURs.

From 1 June 2024, the MHRA will only be accepting online payment of this fee via MHRA Pay prior to submission of an annual safety report. Receipts generated will be sent by email and must be included in the submission as proof of payment.

Failure to provide evidence of payment will result in the submission being made invalid.

The DSUR should include:

- Cover letter listing all EudraCT numbers of trials covered by the DSUR
- Analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit
- Line listing of all Serious Adverse Reactions (SARs) (including all SUSARs) that occurred in the trial(s)
- The Reference Safety Information (RSI)
- An aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)

Full details of what to include in a DSUR can be found in ICH E2F.

Guidance is also available via the MHRA's website for submitting DSURs and a template document (T05) can be found on the WCTU website.

The DSUR will refer to the specific Reference Safety Information (RSI) in use for the trial Investigational Medicinal Product (IMP). For information on how to control the use of the RSI, refer to SOP 17 Part 4 'Reference Safety Information'.

For **Type A** studies approved under the notification scheme, the Short form DSUR can now be used using the HRA CTIMP APR report form which can be found on the HRA Progress reports website. Phase 4 national (UK only) trials of licensed products that commanded a low fee from the MHRA, and where all participants have completed treatment and are only in follow-up are also suitable for submission of a short format DSUR.

A cover letter is required to state that the submission is an APR in lieu of a full DSUR (also ensure the EudraCT number (if applicable), and CTA reference number are included within the letter). A list of all Serious Adverse Reactions is required in section 6 of the APR.

For University of Warwick sponsored studies, copies of DSURs/APRs should be provided to the Sponsor's Office in R&IS via sponsorship@warwick.ac.uk.

### 4.3.3 Safety Reports

Routine safety information is reported in the annual progress reports (see section 4.3.1), but serious adverse events (SAEs) which are both related to the study intervention and deemed to be unexpected are required to be reported to the REC (and the MHRA in the case of CTIMPs) within specified timelines.

Full details are available in Warwick SOP 17 'Safety Reporting' Parts 1 (for CTIMPs) and part 2 (for other research).

For University of Warwick sponsored studies, copies of expedited safety reports should be provided to the Sponsor's Office in R&IS via sponsorship@warwick.ac.uk.

### 4.3.4 Suspend a study temporarily

If a study is temporarily halted, you must notify the relevant NHS REC and MHRA (as applicable) immediately or at least within 15 days. The suspension may involve a single site, multiple sites or all sites depending on the reason for suspension. In all cases of temporary suspension, ensure notifications are sent to all relevant groups e.g., study funder, Trial Management Group (TMG) and Trial Steering Committee (TSC) to detail the decisions made to suspend or restart a study.

For CTIMP applications that have gained approval via the Combined Review process, refer to the HRA website for guidance.

The notification relating to a temporary suspension for CTIMPs not approved via Combined Review should be made as a substantial amendment and be submitted using MHRA Submissions via the Human Medicines Tile. Select 'Clinical Trial' as the Regulatory Activity and 'CT – Amendment' from the Regulatory sub activity dropdown list. A clear explanation of what has been stopped, the number of sites involved and the reasons for the suspension must be given.

All other notifications should be made as a substantial amendment using the amendment tool in IRAS (see SOP 6 'Amendments to Approved Study Documents').

To restart a study that has been temporarily suspended a request must be made as a substantial amendment using the amendment tool, providing evidence that it is safe to restart the study.

For studies managed by WCTU, checklists for recommencing trial recruitment have been developed and should be followed after a temporary suspension to ensure the site has capacity to re-start. See documents C08 and G26 on the WCTU website Templates page

### 4.3.5 Early termination of a study

Complete the end-of-study declaration form and include a brief explanation of the reasons for ending the study.

There are separate forms for use in clinical trials of investigational medicinal products (CTIMPs) which can be found on the MHRA website, and here for all other research.

The form should be emailed to the relevant REC for all studies. For CTIMPs that have gone through the Combined Review process, refer to the HRA website for details of how to submit.

Declaration forms for all other CTIMPs must be submitted using the MHRA's submission portal within 15 calendar days of the date of termination. To submit via the portal, select 'Clinical Trial' as the Regulatory Activity and 'CT –EOT' from the Regulatory sub activity dropdown list.

### 4.3.6 Declaration of the End of the Study

The end of the study must be defined in the protocol and is usually the date of the last visit of the last participant or the completion of any follow-up monitoring and data collection, not the completion of data analysis or publication of the results. (Any change to the protocol's definition of the conclusion of the trial should be notified to the NHS REC and the MHRA (where applicable) as a substantial amendment).

The NHS REC which gave a favourable opinion must be informed in writing of the end of the trial within 90 days of its conclusion using the HRA 'declaration of the end of a study' form.

For CTIMPs, the same end of trial declaration form is used to notify both the REC and the Medicines & Healthcare products Regulatory Agency (MHRA).

For trials submitted through the Combined Review process, the end of trial form must be completed and submitted in the new part of the Integrated Research Application System (IRAS). This automatically submits the notification to the REC and MHRA.

For other CTIMPs, the Declaration form should be sent to the MHRA via the MHRA's submission portal by the CI or their delegate within 90 calendar days of the conclusion of the trial.

For CTIMP and IMP/Device trials that were not submitted through combined review, complete the form available on the MHRA website and email this to the MHRA and REC.

For University of Warwick sponsored studies this activity will be delegated by the sponsor to the CI/study team, and a copy of the form should be sent to the sponsor via sponsorship@warwick.ac.uk.

### 4.3.7 Final Report submission

The Make It Public strategy sets out the HRA's commitment to make transparency easy, make transparency the norm and make information public. They have developed a standard dataset on research transparency which will be collected in the study final reports (the final report template).

The new final report form template can be accessed here.

A copy of this report should also be sent to the WCTU QA team: wctuqa@warwick.ac.uk and the study sponsor. For University of Warwick sponsored studies this will be the Sponsor's Office via sponsorship@warwick.ac.uk.

Once the end of study has been declared and the relevant review bodies notified as described above, a final report of the research is required to be submitted.

All project-based research (not research tissue banks or research databases) that has been reviewed by a REC, needs to submit a final report. This report should be submitted to the research ethics service within 12 months of the end of the study.

If approvals were gained via the Combined Review process, the final report form must be submitted in the new part of IRAS.

All other project-based research reviewed by a REC, should use the webform on the HRA website. When completing the final report form, use the guidance next to each question to help you. One of the questions in the final report asks for a lay summary of the results. The HRA will publish this alongside the rest of the research summary on our website. The HRA also provide guidance on how to write lay summaries of results, which you may find helpful when completing this question.

The HRA may also publish aggregate data collected from the final reports on their website, as part of their annual research transparency reporting. This will not contain any personally identifiable information.

For further information about the final report, see the HRA questions and answers page.

The HRA can be contacted if you have any questions, email: research.transparency@hra.nhs.uk

The HRA recognise that commercial sensitivity may be a concern in some sectors and so it is possible for applicants and sponsors to submit a request to the REC to defer publication of the research summary and the full study title on the HRA website. However, the remainder of the research summary record will continue to be published. - See more at: http://www.hra.nhs.uk/resources/during-and-after-your-study/transparency-registration-and-publication/#sthash.z9NPNJZC.dpuf

For further information on all aspects of research transparency requirements, see SOP 28 'Transparency in Clinical Research Studies'.

**List of Abbreviations**

| | |
|---|---|
| **APR** | **Annual Progress Report** |
| **BSREC** | Biomedical and Scientific Research Ethics Committee |
| **CI** | Chief Investigator |
| **CTIMP** | Clinical Trial of Investigational Medicinal Product |
| **CTU** | Clinical Trials Unit |
| **DSUR** | Development Safety Update Report |
| **EudraCT** | European Union Drug Regulating Authorities Clinical Trials Database |
| **GCP** | Good Clinical Practice |
| **HRA** | Health Research Authority |
| **ICH** | International Conference on Harmonisation |
| **IMP** | Investigational Medicinal Product |
| **IRAS** | Integrated Research Application System |
| **MHRA** | Medicines and Healthcare Products Regulatory Agency |
| **QA** | Quality Assurance |
| **REC** | Research Ethics Committee |
| **R&IS** | Research & Impact Services |
| **RSI** | Reference Safety Information |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SOP** | Standard Operating Procedure |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TSC** | Trial Steering Committee |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **WCTU** | Warwick Clinical Trials Unit |